PORPHYRIN DERIVATIVES, PROCESSES FOR OBTAINING THEM, AND THEIR USES IN RADIOIMMUNOTHERAPY

A subject of the present invention is novel porphyrin derivatives, processes for obtaining them, and their uses in radiotherapy or radioimmunotherapy.

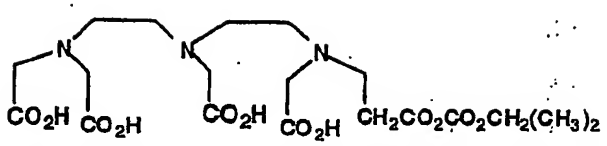
The treatments currently administered in the fight against cancer mainly concern chemical drugs, and the use of sources of radiation. The main problem caused by this type of treatment is the non-specificity of these therapeutic techniques, which as a result leads to the indiscriminate damaging of healthy cells.

The discovery of monoclonal antibodies in the 1970s brought great hope to the fields of cancer diagnosis and therapy. This novel technique in fact appears to be a solution to the problems of non-specificity of antitumor agents. However, monoclonal antibodies capable of recognizing antigens on the surface of tumors do not have sufficient toxicity to destroy them. On the other hand, by combining this protein with an element capable of eliminating the diseased cells, an entity is formed which is very useful, since it is very specific and active. Thus, radioimmunotherapy combines the properties of monoclonal antibodies with that of radioactive metals. The antibody is modified during coupling with a ligand stabilizing the radioelement or directly with the radioelement *(Yuanfang, L.; Chuanchu, W. Pure Appl. Chem.**1991**, 63, 427)*.

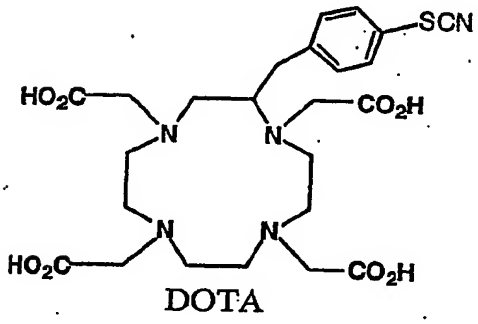
Numerous radioelements have already been the subject of very intensive study (*Yuanfang, L.; Chuanchu, W., mentioned above*) in this field. Bismuth-212 or -213 is an α emitter, i.e. capable of delivering very considerable energy over a very short distance, which makes this metal very attractive for the treatment of small tumor cells. The stakes are therefore high since at present very few α emitters have useful specifications for possible use in radioimmunotherapy (*Wibur, D.S. Antibody, Immunoconj.Radiopharm. **1991**, 4, 85; Feinendegen, L.; McClure, J; Rad. Res.**1997**, 148, 195*).

The first studies relating to the coupling of a bismuth complex with a monoclonal antibody and its behaviour in vitro, were carried out in 1986 by Kozak's team (*Kozak, R.; Atcher, R.; Gansow, O.; Friedman, A.; Hines, J.; Waldmann, T; Proc. Natl. Acad. Sci. USA **1986**, 83*).

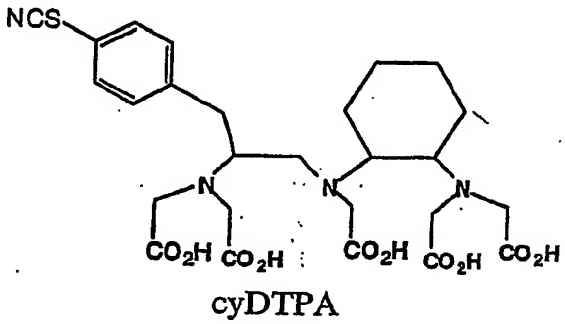
These first very encouraging investigations were carried out with the isobutylcarbonic anhydride of DTPA as a complexing agent, the formula of which is indicated below.



Subsequently, other types of ligands were synthesized in order to perfect the metal coordination sphere and to induce greater stability of the complexes formed. Examples are illustrated hereafter with DOTA and cyclohexylbenzyl DTPA (cyDTPA).



DOTA



cyDTPA

The cyDTPA represented above is at present the most promising ligand. The metallation of this ligand is very rapid (*Brechbiel, M.; Pippin, C.; McMurry, T.; Milenic, D.; Roselli, D.; Colcher,D.; Gansow,O.J. Chem. Soc., chem. Soc.* ***1991****, 1169*), and the complex formed is relatively stable *in vivo*.

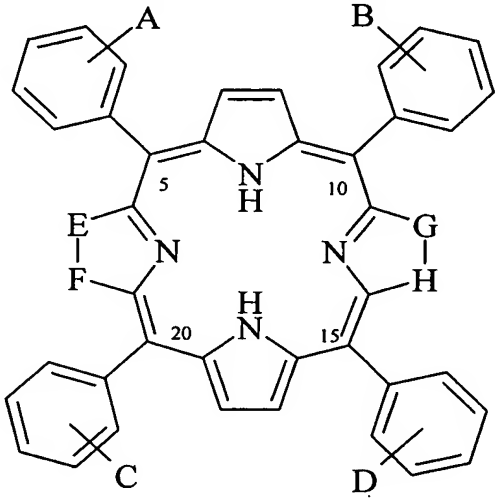
The choice of porphyrins as ligands is not insignificant since studies report a preferential accumulation of porphyrins in tumors (Moan, J.; Berg, K. Photochem. Photobiol. **1992**, 55, 931), and their biocompatible character. Moreover, this macrocycle has unique properties due to its disc shape and its relative rigidity.

Preliminary studies, carried out by the Inventors, on so-called planar porphyrins, such as octaethylporphyrin, have shown that the metal was situated above the plane of the porphyrin. The counter-anion is important since, in the isolated complexes, the metal is linked to triflate and nitrate anions (oxygenated counter-anion). The Inventors have also attempted to metallate tetraphenylporphyrin with different bismuth salts and in particular bismuth chloride, when the reaction is carried out under argon, and followed by UV-visible spectroscopy, the start of metallation is noted but most of the starting ligand is not consumed, and the complex obtained is not stable.

The purpose of the present invention is to provide new compounds allowing the complexation of radioelements such as the α emitters, and more particularly bismuth, making it possible to form complexes with the above-mentioned radioelements which are more stable compared with the compounds of the prior art, by the presence of pre-organized handles modifying neither the geometry of the tetrapyrrolic nucleus nor its electronic properties.

A purpose of the invention is also to provide novel pharmaceutical compositions liable to be used in radiotherapy or radioimmunotherapy.

A subject of the present invention is the compounds corresponding to the following general formula (I):



in which:

– when A forms a chain with C, the so-called A-C chain, of formula (1) below:

$$-X-Y-C_6H_4-(CH_2)_{n1}-U-(CH_2)_{n2}-C_6H_4-Y-X- \qquad (1)$$

in which:

. when X represents NH, O, CO or CH_2, Y represents respectively CO, CH_2, NH, or O,

. n_1 and n_2, independently of one another represent an integer comprised between 1 and 3,

. U represents a group of the C(Z,W) or $N(CHR_a-COOR_b)$ form, in which

. Z represents:

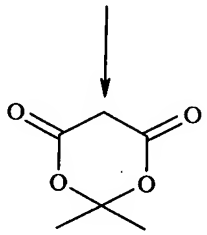
* an electroattractive group such as CN, NO_2, or CO_2^-,

* or a $CH_2NR_1R_2$ group, in which R_1 and R_2 represent, independently of one another, H, or a linear, branched, or cyclic alkyl group, with 1 to 8 carbon atoms, or an aryl or alkylaryl group, or a specific antibody, if appropriate linked to the CH_2N part of said group via a spacer,

* or an aryl group substituted by an SO_3R_3, SO_2R_3, p-NO_2 or o-NO_2 function, in which R_3 represents H, or a cation chosen from the alkali metals such as Na^+, or K^+, or R_3 represents an NR_4R_5 group in which R_4 and R_5 represent, independently of one another, a linear, branched, or cyclic alkyl group, with 1 to 8 carbon atoms, or R_3 represents a para-nitro aryl group,

. W represents a CO_2^- or $COOR_6$ group in which R_6 represents H or a linear, branched, or cyclic alkyl group, with 1 to 8 carbon atoms, or an aryl group, or an alcohol depopulated of electrons such as a para-nitro phenol or ortho-para-nitro phenol group,

. or Z and W form in combination with the carbon atom which carries them (indicated by an arrow hereafter) a ring designated Meldrum's acid with the following formula:



. R_a corresponds to the definition previously given for R_1, or can also preferably represent the side chain of a natural or modified amino acid,

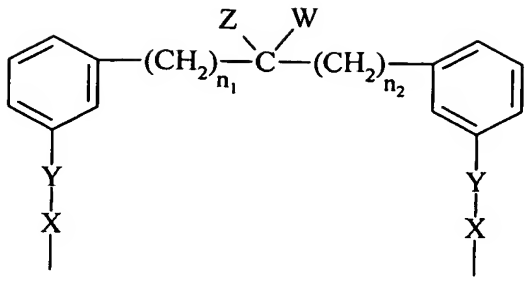
. R_b corresponds to the definition previously given for R_1,

then B forms a chain with D, the so-called B-D chain, of the abovementioned formula (1), said A-C, and B-D chains, being situated independently of one another, above (position α) or below (position β) the porphyrin macrocycle plane,

– or when A forms a chain with D, the so-called A-D chain, of the abovementioned formula (1), then B forms a chain with C, the so-called B-C chain, of the abovementioned formula (1), one of said A-D or B-C chains being situated above (position α) the porphyrin macrocycle plane, whilst the other A-D or B-C chain, is situated below (position β) the porphyrin macrocycle plane,

– E represents in combination with F, and H represents in combination with G, independently of each other, CH=CH, or CH_2-CH_2.

A more particular subject of the invention is the abovementioned compounds of formula (I), characterized in that the chain formations of formula (1) are chosen from the following:



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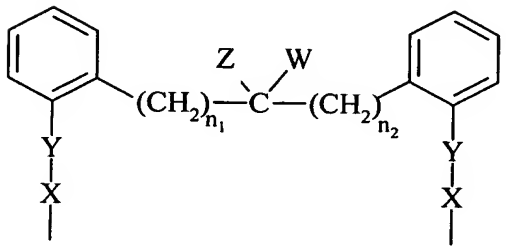

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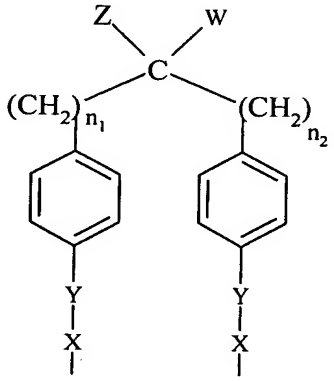


in which the Z and W groups are:

– either directed towards the interior of said compounds and are situated above or below the porphyrin macrocycle plane according to whether said chain formations of formula (1) are situated respectively in α position or in β position, and are respectively designated Ziα and Wiα, or Ziβ or Wiβ,

– or directed towards the exterior of said compounds, and are respectively designated Ze and We.

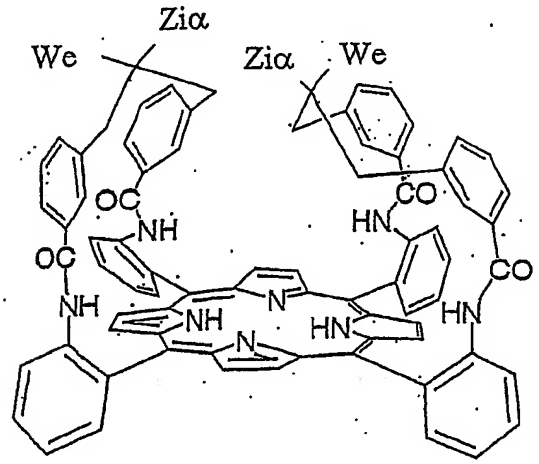
A more particular subject of the invention is also the compounds as defined above, characterized in that A, B, C, and D are in ortho position, as well as those characterized in that E represents in combination with F, and H represents in combination with G, CH_2-CH_2.

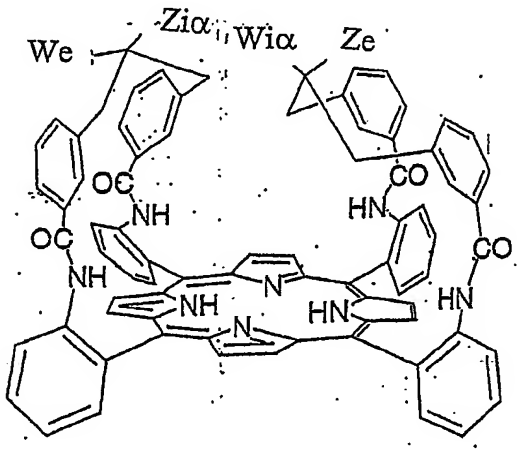
The invention more particularly relates to the compounds as defined above, characterized in that A forms with C, and B forms with D, chain formations of formula (1) respectively designated A-C and B-D, these two chain formations being situated in a, said compounds also being designated compounds of formula (Ia).

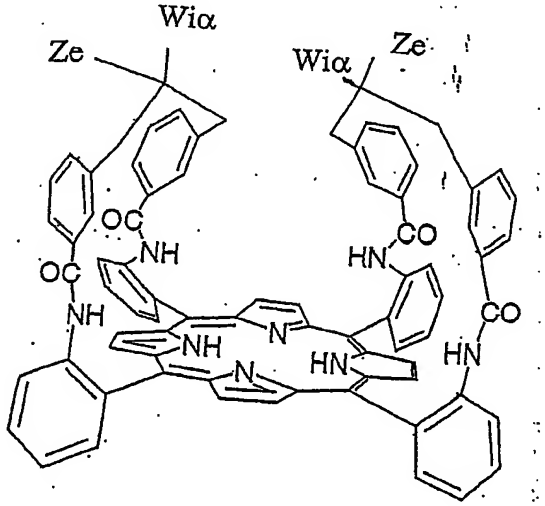
In this respect, a more particular subject of the invention is the abovementioned compounds of formula (Ia), characterized in that:

- the A-C and B-D chain formations each comprise a Ziα group and a We group,
- or the A-C chain formation comprises a Ziα group and a We group, whilst the B-D chain formation comprises a Ze group and a Wiα group,
- or the A-C and B-D chain formations each comprise a Ze group and a Wiα group.

Preferred compounds of formula (Ia) are those characterized by the following formulae:







The invention also relates to the compounds of formula (I) as defined above, characterized in that A forms with C an A-C chain formation of formula (1) situated in the α position, and B forms with D, a B-D chain formation of formula (1) situated in the β position, said compounds also being designated compounds of formula (Ib).

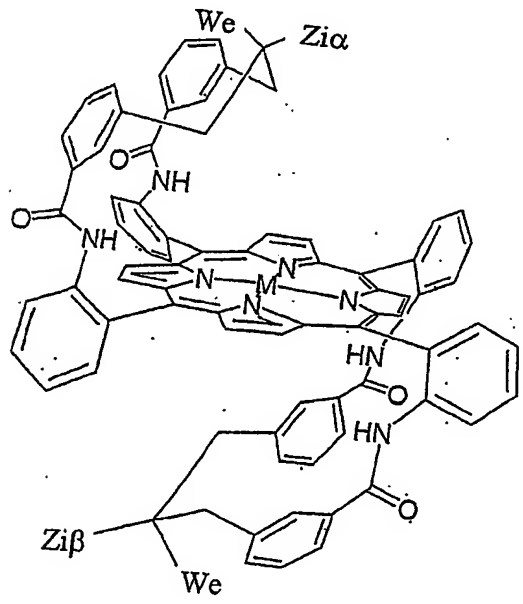
In this respect, a more particular subject of the invention is the abovementioned compounds of formula (Ib), characterized in that:

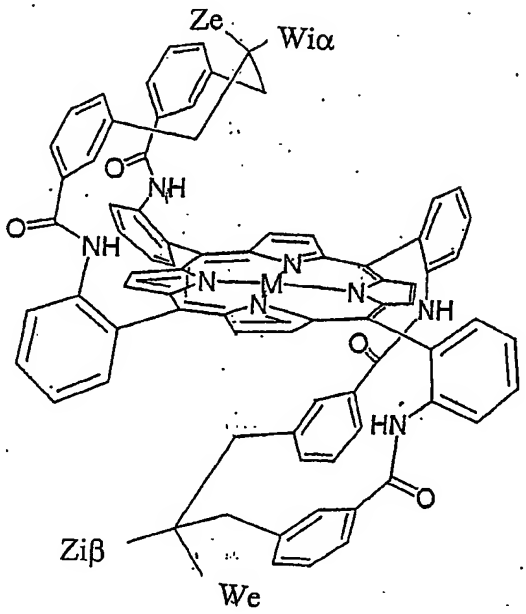
– the A-C chain formation comprises a Ziα group and a We group, whilst the B-D chain formation comprises a Ziβ group and a We group,

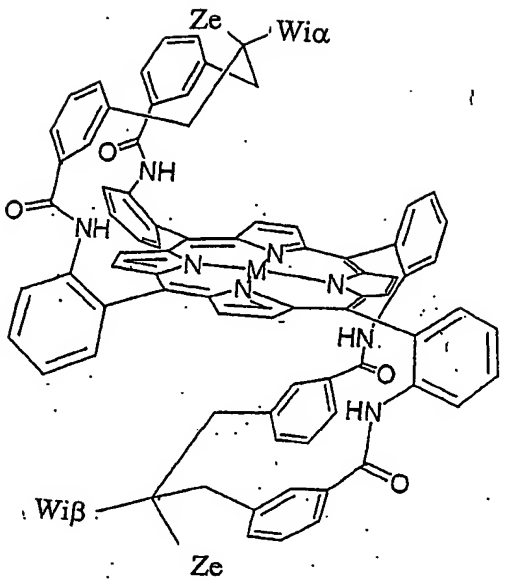
– or the A-C chain formation comprises a Ze group and a Wiα group, whilst the B-D chain formation comprises a Ziβ group and a We group,

– or the A-C chain formation comprises a Ze group and a Wiα group, whilst the B-D chain formation comprises a Ze group and a Wiβ group.

Preferred compounds of formula (Ib) are those characterized by the following formulae:







The invention also relates to the compounds of formula (I) as defined above, characterized in that A forms with D an A-D chain formation of formula (1) situated in position β, and B forms with C a B-C chain formation of formula (1) situated in position α, said compounds also being designated compounds of formula (Ic).

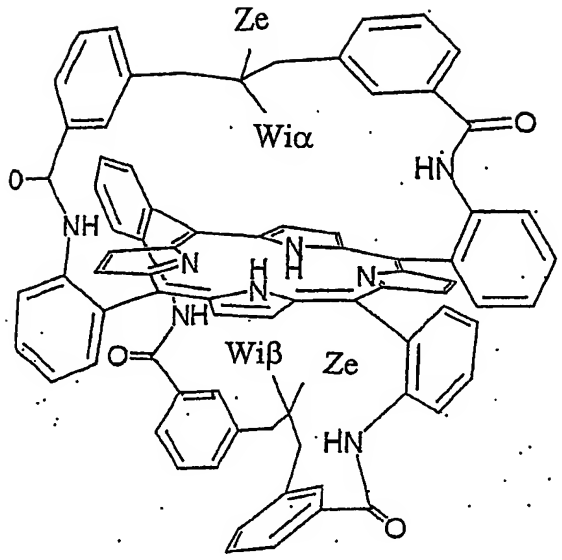
In this respect, a more particular subject is the abovementioned compounds of formula (Ic), characterized in that:

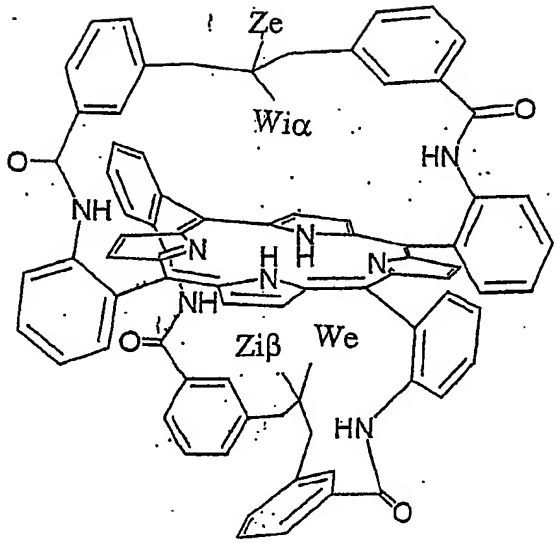
– the A-D chain formation comprises a Ze group and a Wiβ group, whilst the B-C chain formation comprises a Ze group and a Wiα group,

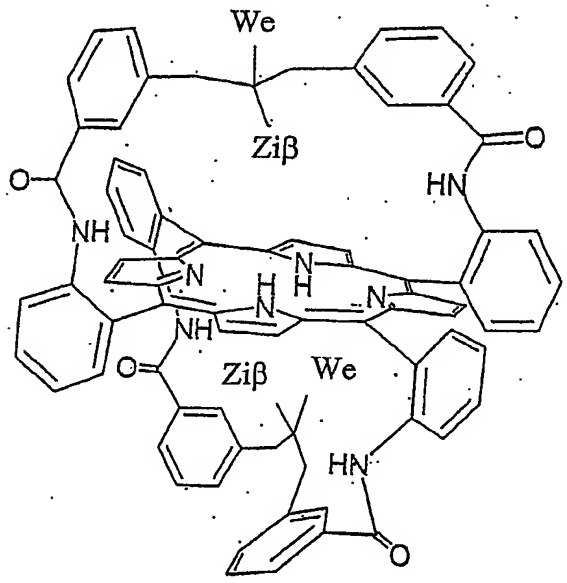
– or the A-D chain formation comprises a Ziβ group and a We group, whilst the B-C chain formation comprises a Ze group and a Wiα group,

– or the A-D and B-C chain formations each comprise a Ziβ group and a We group.

Preferred compounds of formula (Ic) are those characterized by the following formulae:







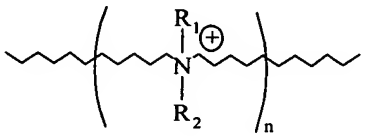
The invention also relates to the compounds of formula (I), and more particularly those of formula (Ia), (Ib), and (Ic), as defined above, in which Z represents a

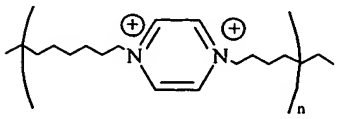
$CH_2NR_1R_2$ group, in which at least one of R_1 and R_2 represent a specific antibody, if appropriate linked to the CH_2N part of said group via a spacer.

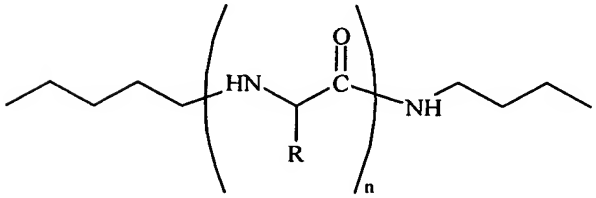
Such antibodies can be chosen from those mentioned at the Roche Symposium, held on Thursday 7th June 2001, Paris, EUROCANCER 2001, in particular from the following antibodies:

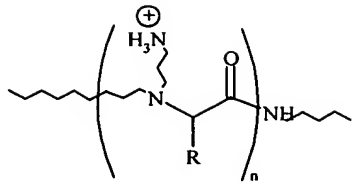
- J591: murine IgG2A, anti-PSMA (Prostate Specific Membrane Antigen) expressed on carcinomatous human prostate cells,
- B4: murine IgG1, anti-CD19 expressed on Ramos and Daudi lymphoma cells,
- HuM195: humanized IgG1, anti-CD33 expressed on human leukemia HL60 cells,
- 3F8: murine IgG3, anti-CD2 expressed on human neuroblastoma NMB7 cells,
- Herceptin, trastuzumab: humanized IgG1, anti-HER2 expressed by human MCF7 breast and SKOV3 ovarian carcinoma cells,
- 35A7: directed against the carcinoembryonic antigen (CEA),
- Basiliximab, Simulect: entirely chimeric, anti-CD25, used in the prevention of kidney graft rejection,
- Gentuzumab ozogamicin: entirely humanized, anti-CD33,
- Rituximab, Tositumomab: chimeric, anti-CD20, antigen expressed in more than 95% of neoplasic lymphocytes,
- BL22: anti-CD22,
- SGN-10: anti-LeY, expressed by different types of carcinoma, in particular by digestive epithelial cells and by pancreatic acinus cells.

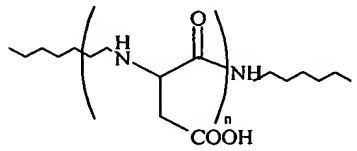
By way of illustration, the abovementioned spacer is chosen from the groups of the following formulae:

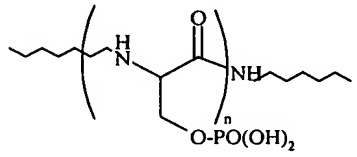


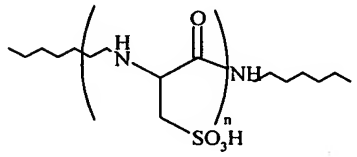


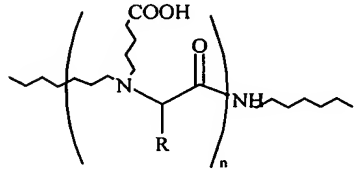


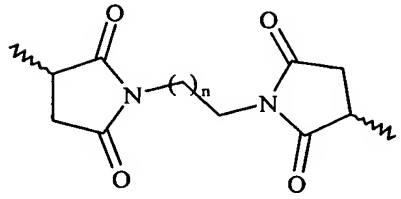


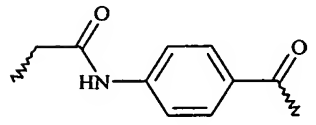


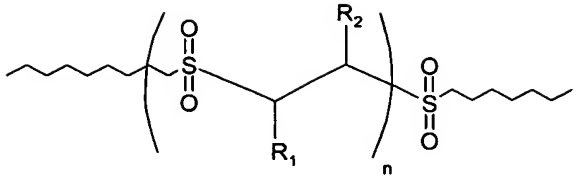


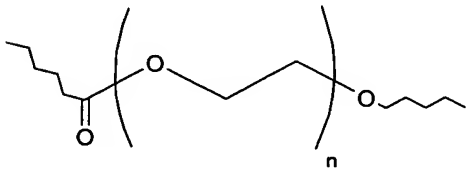


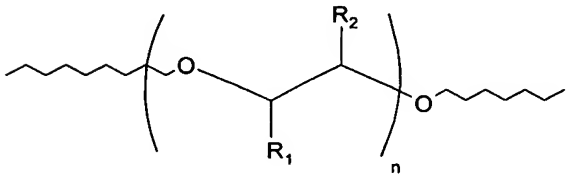


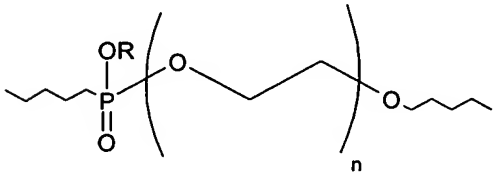


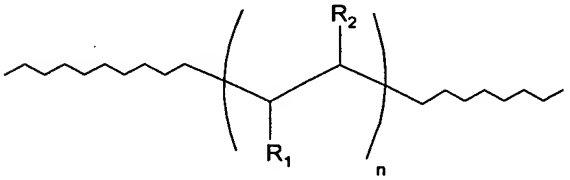


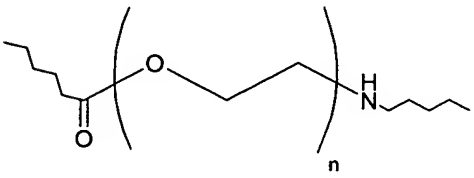


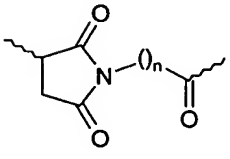


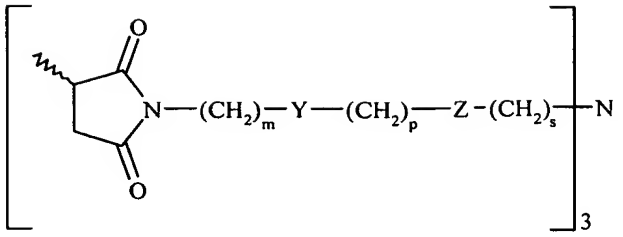


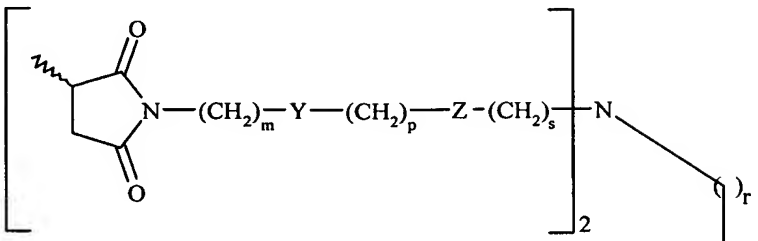


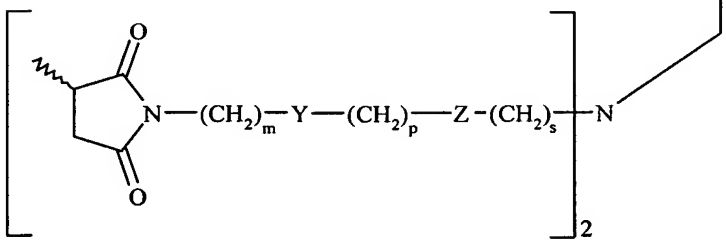


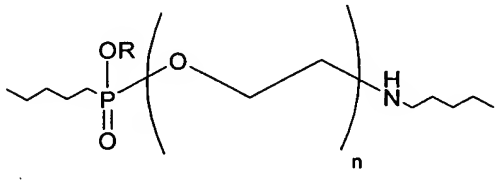


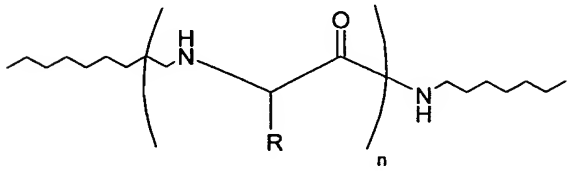












in which n and r represent an integer varying from 1 to 10, R_1 and R_2 represent, independently of one another, H, or a linear, branched, or cyclic alkyl group, with 1 to 8 carbon atoms, or an aryl or alkylaryl group, R represents one of the side chains of the 20 natural amino acids, Y and Z represent heteroatoms such as O or S, m, p and s, independently of each other, represent 0 or an integer varying from 1 to 10.

The invention also relates to complexes between a compound as defined above, and a radioelement chosen from the α emitters, or a divalent or trivalent metallic element.

A more particular subject is the abovementioned complexes between a compound as defined above, and an α-emitter radioelement chosen from bismuth-212 or -213, actinium-225, or astatine-211.

The invention also more particularly relates to the abovementioned complexes between a compound as defined above, and a divalent or trivalent metallic element chosen from Y(III), In(III), Cd(II), Mg(II), Mn(III), Fe(III), B(III) and the lanthanides.

In the complexes of the invention, the metals are situated in the centre of the porphyrin nucleus of the abovementioned compounds, but not necessarily in the porphyrin plane, and are bound to the nitrogen atoms of said nucleus by covalent bonds, two of which are of dative type.

A subject of the invention is also any pharmaceutical composition characterized in that it comprises a complex as defined above, in combination with a pharmaceutically acceptable vehicle.

Advantageously the pharmaceutical compositions according to the invention are presented in a form which can be administered by intravenous route.

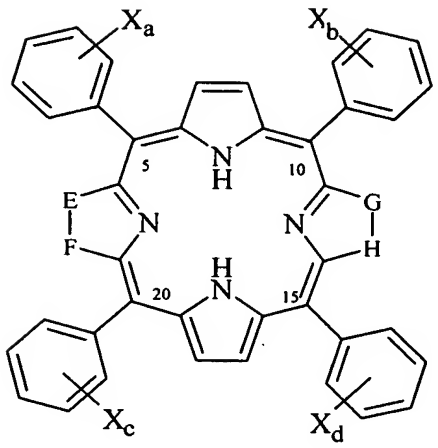
Preferably, the abovementioned pharmaceutical compositions are characterized in that the dosage is approximately 15 to 50 mCi per patient divided into 3 to 6 fractions over 2 to 4 days.

The invention also relates to the use of complexes as defined above for the preparation of a medicament intended for the treatment of cancers, or for the preparation of compositions intended for medical imaging.

A more particular subject of the invention is the use of complexes as defined above, for the preparation of a medicament intended for the treatment of tumorous small-cell cancers, such as acute myeloid leukemia, non-Hodgkin's lymphomas, bronchopulmonary dysplasias, metastatic breast cancers, colorectal cancers, lymphomas, and pathologies in which the following antigenic units: CD52, CD22, CD20, HLA-DR, CD33, LE-Y, Ep-CAM, ACE, CAN, EGFR, KSA, VEGF, HER2, GD2, tenascin are involved.

The invention also relates to a process for preparing the abovementioned compounds of formula (I), characterized in that it comprises the following stages:

- treatment of the compound of the following formula (II)



in which X_a, X_b, X_c, and X_d, represent NH_2, OH, COOH or CH_2Cl, and E, F, G, and H being defined above, said compound being such that:

. X_a, X_b, X_c, and X_d, are in α position in the case of the synthesis of compounds of formula (Ia),

. X_a, and X_c, are in α position, and X_b and X_d are in β position in the case of the synthesis of compounds of formula (Ib),

. Xa, and Xd, are in β position, and X_b and X_c are in α position in the case of the synthesis of compounds of formula (Ic),

with a compound of formula Y_a-C_6H_4-CH_2Cl in which Y_a represents COOH, CH_2Cl, NH_2, or OH respectively,

– a stage of treatment of the compound obtained at the preceding stage with a compound of formula Z-CH_2-W in which Z and W are as defined above, which leads to the obtaining of a compound of formula (I) the different variants of formulae (Ia), (Ib), and (Ic) of which are separated by purification, in particular by low pressure chromatography on silica gel, or preparative HPLC.

The above-mentioned complexes are obtained by bringing together the compounds of formula (I) with a radioelement as defined above.

The description is further illustrated by the detailed description which follows of particular compounds of the invention, and of the process for obtaining them.

With regard to bismuth, given the properties of this metal, namely its azophilic and oxophilic character and high coordination number (up to nine atoms), the Inventors have synthesized models corresponding as well as possible to the requirements of the metal. In fact, the nitrogen atoms originating from the porphyrin ring are involved in the complexation of the metal and the handles bring groups possessing oxygen atoms to the

metal. Moreover, it should be noted that the ligand forms a cage capable of accepting and stabilizing the metal. Figure 1 represents the basic skeleton of ligands, as well as the process for synthesis of the latter.

The provision of this type of porphyrin compared with picket porphyrins (*Buckingham, D.; Clarck ,C.; Webley, W.J. Chem. Soc. Chem. Com.* ***1981****, 192, Michaudet, L.; Richard, P.; Boitrel, B. Chem. Commun.* ***2000****, 1589-1590, Michaudet, L. doctoral thesis, University of Burgundy,* ***7/12/2000****, Dijon*) resides in the pre-organization of the handle (or handles). The fact that the pickets or the handles are pre-organized makes it possible to have a carboxylic-type group (acid, or ester) just above the metal. Moreover, thanks to the modularity of the synthesis, it is possible to envisage varying the number of coordinating groups.

This diagram, although representing the basis for the present invention, is not applicable and has already been published (*Didier, A.; Michaudet, L.; Ricard, D.; Baveux Chambenoit, V.; Richard, P.; Boitrel, B. Eur.J. Org. Chem.* ***2001****, 1917-1926*), for two different reasons. On the one hand, after saponification of the ester functions (and consequently decarboxylation), there is no control of the position of the residual acid function. On the other hand, these porphyrins possess no subsequent functionalization point, necessary for grafting to an antibody, or for making the compound hydrosoluble.

On the other hand, this type of ligand possesses a very rigid structure, with a predetermined geometry, which should increase the stability of the complex formed. It is in fact for reasons of stabilization of the metallic element that the synthesis of the cyclohexylbenzyl DTPA was developed, this ligand being more rigid in nature than DTPA *(Brechbiel, M.; W.; Gansow, O. A. J. Chem. Soc., Perkin Trans.I* ***1992****, 1173).*

In order to avoid obtaining two different products as represented in Figure 1, the same synthesis strategy was applied to the $\alpha\alpha\beta\beta$ isomer (Figure 2).

The obtaining of a radio-crystallographic structure clearly shows that the ethoxycarbonyl group directed towards the interior of the porphyrin is suitably maintained above the metal (Figure 3).

The invention consists of using ethyl cyanoacetate ($NC\text{-}CH_2\text{-}CO_2Et$) instead of ethyl malonate during the synthesis described in Figure 1, and applying it to the $\alpha\alpha\beta\beta$ and $\alpha\beta\alpha\beta$ isomers in addition to the $\alpha\alpha\alpha\alpha$ isomer. In the case of the $\alpha\alpha\alpha\alpha$ isomer, three porphyrins are thus obtained, from which porphyrin **5** can be purified, which possesses the ester function oriented towards the interior (Figure 4).

This orientation of the ester function makes it possible to make these compounds useable for a coordination of metals such as bismuth (III) or the lanthanides. By proton spectroscopy, the structure **5** can be immediately attributed to a molecule due to its symmetry and the significant shielding undergone by the ethyl groups oriented towards the interior of the cavity. In fact, by analogy with the NMR spectroscopy spectrum of compound **2**, compounds **5** and **6** can be easily discerned. Moreover, compound **7** represents a ligand of the same conformation, but with a single ethoxycarbonyl group for coordinating the metal.

Therefore, after saponification in a first phase, and reduction of the CN function to CH_2-NH_2 in a second phase, products are obtained the conformation of which is perfectly known and which possess two subsequent functionalization points (Figure 5).

As described for Figure 2, this variant applied to the $\alpha\alpha\beta\beta$ atropisomer will give rise to the six ligands represented in Figure 6.

The usefulness of the porphyrins, represented in Figure 6, resides in the identity of their two faces both for the coordination of the metal and for grafting to an antibody. This structure can be used for the construction of bispecific monoclonal antibodies. The latter result from the assembly of two "semi-antibodies" on a bifunctional spacer (such as a bismaleimide-type derivative). The porphyrin **16** can be considered in this context both as a complexing element and as a bridging element as represented diagrammatically in Figure 7.

It should be noted that the porphyrin has been grafted onto two Fab' fragments via a bifunctional spacer called SIAB for (N-succinimidyl(4-iodoacetyl)-aminobenzoate. These two fragments can be of different specificity in order to improve the recognition specificity.

It should also be noted that two thiol functions are presented on the Fab' fragment, and that as a result different connection diagrams are possible between the porphyrin and the antibody.

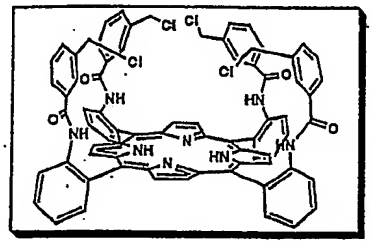
Finally, the fact of obtaining compound **3** (Figure 1) from the $\alpha\alpha\alpha\alpha$ atropisomer demonstrates that the same reaction sequence applied to the $\alpha\beta\alpha\beta$ atropisomer gives rise to compound **18**, of *bis-ansa* type (Figure 8). This type of compound is useful for prohibiting any intermolecular interaction such as the formation of dimers as described for aliphatic picket porphyrins (Michaudet et al., 2000, mentioned above).

Molecular dynamic modelling of porphyrin **18** shows that the pre-organization of this superstructure perfectly directs one of the two carbonyl functions (belonging to the

ester) towards the coordination centre. This point signifies that it is again possible to differentiate the "internal" from the "external" ethoxycarbonyl group, and therefore that if Stage ii) is carried out with ethyl cyanoacetate, three porphyrins **19**, **20** and **21** (Figure 9) are again obtained.

EXPERIMENTAL PART

α-5,10,15,20-Tetrakis{2-[(3-chloromethyl)benzoylamido]phenyl}porphyrin: 1



$C_{76}H_{54}Cl_4N_8O_4$

MW: 1285.10

0.2 g of TAPP 4.0 (0.29 mmol), 0.5 mL of triethylamine and 20 mL of THF, are introduced into a 100-mL two-necked flask under argon. 0.34 mL (2.3 mmol) of 3-(chloromethyl) benzoic acid chloride are added using a syringe. The reaction is carried out at ambient temperature over 12 hours, then the reaction mixture is evaporated, followed by purification by chromatography on a silica column and the desired product is eluted with a mixture of methanol in dichloromethane (0.1%) then isolated with a yield of 81% (0.3 g, 0.23 mmol).

Elemental analysis: $C_{76}H_{54}N_8Cl_4O_4$, calculated (%): C, 71.03; H, 4.24; N, 8.72; found (%): C, 70.89; H, 4.11; N, 8.83

Mass spectrometry (FAB): m/z = 1284.9 $[M]^{+\cdot}$

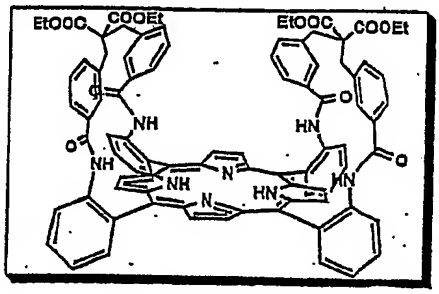
Infra-red (KBr, cm^{-1}): 1680 $(C=O)_{amide}$, 3415 (NH)

Mass spectrometry HRMS: calculated m/z = 1304.2920 for $C_{56}H_{46}N_8O8Na$ measured m/z = 1304.2909

NMR ^1H (δ ppm, $CDCl_3$, 300K: 8.99 (s, 8H, β-pyr.); 8.89 (d, J = 8.3 Hz, 4H, aro.); 8.02(dd, J = 1.3 Hz, J =7.5 Hz, 4H, aro.); 7.92 (td, J = 1.3 Hz, J = 8.3 Hz, 4H, aro.); 7.81 (s, 4H, -NHCO); 7.59 (td, J = 0.9 Hz, J = 7.6 Hz, 4H, aro.); 6.52 (broad s, 4H, $aro_{pick.}$); 6.51 (d, J = 8.1 Hz, 4H, aro_{pick}); 6.40 (d, J = 7.7 Hz, 4H, aro_{pick}); 6.40 (d, J = 7.7 Hz, 4H, aro_{pick}); 6.00 (t, J = 7.7 Hz, 4H, aro_{pick}); 3.23 (s, 8H, $-CH_2-$); -2.47 (s, 2H).

NMR ^{13}C (δ ppm, $CDCl_3$, 300K): 165.2; 138.8; 137.5; 135.6; 135.2; 132.4; 131.3; 131.0; 130.6; 128.4; 126.6; 126.0; 123.9; 121.3; 115.5; 44.6.

α-5,10: α-15,20- Bis-{2,2' -[3,3'-(2,2-(diethoxycarbonyl)propane-1,3-diyl) dibenzoylamido]diphenyl}porphyrin: 2



$C_{90}H_{74}N_8O_{12}$

MW: 1459.60

18 mg (0.8 mmol) of sodium is dissolved in 5 mL of absolute ethanol in a 50-mL three-necked flask under argon. After ½ hour ethyl malonate (118µl, 0.8 mmol) is added using a syringe. 50 mg of 1 (0.04 mml), are previously dissolved in 10 mL of THF, then added dropwise to the reaction mixture. The crude product is evaporated at the end of 24 hours, then deposited on a silica column. The product is eluted with a mixture of $MeOH/CH_2Cl_2$ and obtained with a yield of 80% (46 mg, 0.03 mmol).

Elemental analysis: $C_{90}H_{74}N_8O_{12}\bullet CH_2Cl_2$, calculated (%): C, 70, 76; H, 4.96; N, 7.25 found (%): C, 70.68; H, 4.06; N, 6.93

Infra-red (KBr, cm^{-1}): 1726 $(C=O)_{ester}$, 1683 $(C=O)_{amide}$, 3417 (NH)

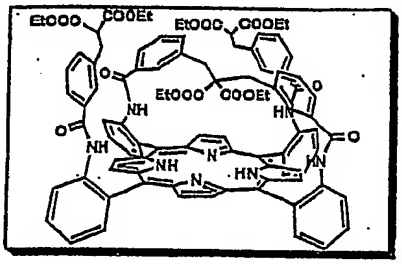
Mass spectrometry (FAB): m/z = 1459.1 $[M]^{+\cdot}$

Mass spectrometry HRMS: calculated m/z = 1481.5335 for $C_{90}H_{74}N_8NaO_{12}$; measured m/z = 1481.5324

NMR ^1H (δ ppm, $CDCl_3$, 300K): 8.92 (s, 4H, β-pyr); 8.87 (s, 4H, β-pyr.); 8.69 (d,J = 8.4 Hz, 4H, aro.); 7.91 (td, J = 7.8 Hz, J = 1.3 Hz, 4H, aro.); 7.79 (dd, J = 7.5 Hz, J = 1.2 Hz, 4H, aro.); 7.49 (td, J = 7.5, 4H, aro.); 7.41 (s,4H, -NHCO); 7.07 (d, J = 7.9 Hz 4H, aro_{pick}); 6.65 (d, J = 7.5 Hz, 4H, $aro_{pick.}$); 6.59 (s, 4H, $aro_{pick.}$); 6.39 (t, J = 7.7 Hz, 4H, $aro_{pick.}$); 3.98 (q, J = 6.9 Hz, 4H, $-\mathbf{CH_2}CH_3$); 3.53 (q, J = 7.1 Hz, 4H, $-\mathbf{CH_2}CH_3$); 2.38 (d, J = 13.8,4H, $-CH_2-$); 2.19 (d, J = 13.8 Hz, 4H, $-CH_2-$); 1.09 (t, J = 6.9Hz, 6H, $-CH_2\mathbf{CH_3}$); 0.64 (t, J = 7.1 Hz, 6H, $-CH_2\mathbf{CH_3}$); -2.95 (s, 2H).

NMR ^{13}C (δ ppm, $CDCl_3$, 300K): 170.9; 170.5; 166.7; 138.3; 136.5; 135.9; 134.7; 133.2; 132.1; 130.3; 128.6; 127.8; 126.3; 123.7; 122.7; 115.4; 31.7; 61.7; 61.4; 40.7; 14.4; 13.8.

α-5,15-{2,2'-[3,3'-(2,2-(diethoxycarbonyl)propane-1,3-diyl)dibenzoylamido] diphenyl}: α-10,20-Bis-{2,2'-[3,3'-(1,1-(diethoxycarbonyl)ethane-2yl) benzoylamido]phenyl} porphyrin: 3



$C_{97}H_{86}N_8O_{16}$
MW: 1619.77

The same operating method as that adopted in order to synthesize the preceding molecule is implemented. Starting with 0.89 of sodium (40 mmol) and 5.9 mL of ethyl malonate (40 mmol) in 35 mL of absolute ethanol, 50 mg (0.04 mmol) of porphyrin **1** dissolved in 10 mL of THF is added. The crude product is chromatographed on a silica column and the desired product is eluted with a mixture of pentane/chloroform (5/100) with a yield of 74% (47 mg, 0.03 mmol).

Elemental analysis: $C_{97}H_{86}N_8O_{16}\bullet H_2O$,calculated (%): C,71.14; H,4.42; N, 6.84; found (%): C, 69.92; H, 4.25; N, 6.63

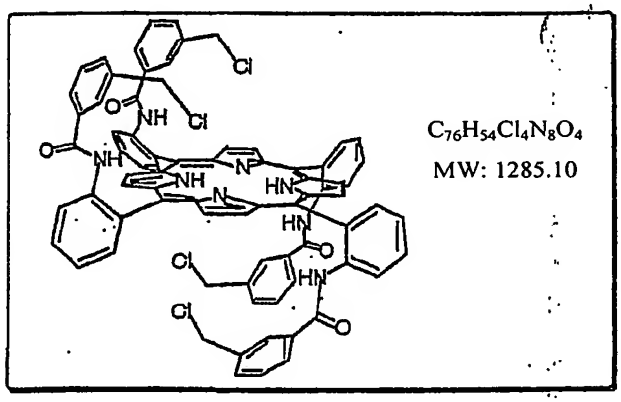
Mass spectrometry (MALDITOF): m/z = 1619.3 $[M]^{+\cdot}$

Infra-red (KBr, cm^{-1}): 1732 $(C=O)_{ester}$, 1682 $(C=O)_{amide}$, 3416 (NH)

NMR^{1}H (δ ppm, $CDCl_3$, 320K): 9.08 (d, J = 8.44 Hz, 2H, aro); 9.06 (d, J = 4.7 Hz, 4H, β-pyr.); 8.95 (d, J=4.7 Hz, 4H, β-pyr); 8.71 (d, J = 8.4 Hz, aro.); 8.56 (broad s, 2H, -NHCO); 8.04 (dd, J =1.1 Hz, J = 6.9 Hz, 2H, aro.); 7.94 (broad t, J = 6.6 Hz, 4 H, aro., - NHCO); 7.85 (td, J = 1.3 Hz, J = 8.2 Hz, 2H, aro.); 7.69 (d, J = 7.7 Hz, 2H, $aro_{pick.}$); 7.65 (dd, J = 1.3 Hz, J = 7.7 Hz, 2H, aro.); 7.59 (t, J = 7.2 Hz, 2H, aro.); 7.55 (s, 2H, $aro_{pick.}$); 7.47 (t, J = 7.5 Hz, 2H, aro.); 6.97 (t, J = 7.7 Hz, 2H, $aro_{pick.}$); 6.50 (d, J = 7.8 Hz, 4H, $aro_{pick.}$); 6.44 (d, J = 5.7 Hz, 2H, $aro_{pick.}$); 5.88 (t, J = 7.4 Hz, 2H, $aro_{pick.}$); 4.84 (s, 2H, $aro_{pick.}$); 4.09 (m, 8H, $-CH_2-CH_3$); 3.38 (t, J = 7.6 Hz, 2H, $-CH_2CH-$); 2.81 (d, J = 7.6 HZ, 4H, $-CH_2CH-$); 1.63 (s, 4H, $-CH_2-$); 1.17 (t, J = 7.2 Hz, 12H, $-CH_2CH_3$); 0.95 (broad s, 4H, $-CH_2$, CH_3); -0.6 (broad s, 6H, $-CH_2CH_3$); -2.25 (s, 2H).

NMR ^{13}C (δ ppm, $CDCl_3$, 300K): 168.8; 168.1; 166.6; 164.6; 139.2; 138.9; 138.0; 137.7; 136.1; 135.4; 135.2; 133.7; 132.9; 132.5; 131.9; 131.4; 130.6; 130.3; 128.8; 128.7; 128.5; 127.7; 125.8; 123.9; 123.5; 122.6; 120.9; 116.5; 115.1; 62.0; 53.6; 42.0; 34.1; 14.2; 12.0.

α-5,10: β-15,20-Tetrakis{2-[(3-chloromethyl)benzoylamido]phenyl} porphyrin: 4



0.674 g (1 mmol) of ααββ TAPP, 2.22 mL (16 mmol) of triethylamine and 100 mL of THF are introduced into a 250-mL two-necked flask, under argon. 0.71 mL (5 mmol) of 3-(chloromethyl)benzoic acid chloride dissolved in 10 mL of THF are added dropwise. The reaction is carried out at 0°C for 3 hours, then the reaction mixture is evaporated. The residue is purified by chromatography on a silica column, the product is eluted with pure dichloromethane, then isolated with a yield of 86% (1.10g).

NMR ^1H 500 MHz (δ ppm, $CDCl_3$, 300K): -2.52 (s, 2H, NH_{pyr}); 3.52 (d, 4H, *Jo* = 12.1 Hz, $(CH_2)_{benz}$); 3.55 (d, 4H, *Jo* = 12.1 Hz $(CH_2)_{benz}$); 6.39 (t, 4H, *Jo* = 7.7 Hz, aro_{pick}); 6.52 (d, 4H, *Jo* = 8.3 Hz, aro_{pick}); 6.55 (s, 4H, aro_{pick}); 6.74 (d, 4H, J_0 = 7.5 Hz, aro_{pick}); 7.61 (t, 4H, *Jo* = 7.5 Hz, aro); 7.66 (s,4H, NHCO); 7.93 (t,4H, *Jo* = 8.3 Hz, aro); 8.07 (d, 4H, *Jo* = 7.3 Hz, aro); 8.90 (d, 4H, *Jo* = 8.3 Hz, aro); 8.99 (s, 4H, β-pyr); 9.00 (s, 4H, β-pyr).

NMR ^{13}C 125 MHz (δ ppm, $CDCl_3$, 300K): 44.8; 115.4; 121.5; 123.9; 126.3; 126.6; 128.7; 130.7; 131.3; 135.2; 135.5; 137.6; 138.8; 165.2.

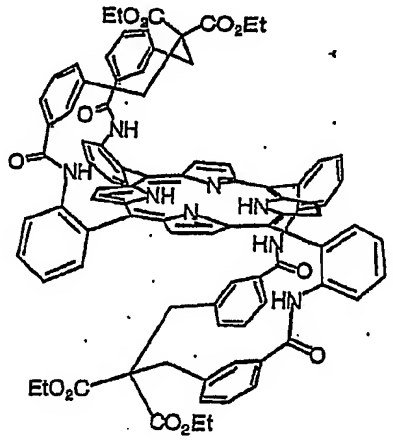
UV-vis (CH_2Cl_2, λ/nm (10^{-3}.ε, $M^{-1}.cm^{-1}$)): 422 (363.8); 515 (20.6); 549 (5.1); 589 (6.2); 646 (2.6).

Mass spectrometry (SMHR, LSIMS) calculated m/z = 1305.2920 $[M+Na]^+$ for $C_{76}H_{54}Cl_4N_8NaO_4$, found 1305.2899.

Elemental analysis: for $C_{76}H_{54}Cl_4N8O_4$, calculated (%): C, 71.03; H, 4.24; N, 8.72; found (%): C, 70.62; H, 4.19; N, 8.94.

Infrared (KBr, υ cm^{-1}): 3420 5NH); 1684 (CO).

α-5,10:β-15,20-Bis{2.2'-[3.3'-(2.2'-(diethoxycarbonyl)propane-1,3-diyl) dibenzoylamido]diphenyl}porphyrin: 5



$C_{90}H_{74}N_8O_{12}$

MW: 1459.60

0.19 mg (8.2 mmol) of sodium is dissolved in 30 mL of absolute ethanol in a 50-mL three-necked flask under argon. After 30 minutes, ethyl malonate (1.24 mL, 8.2 mmol) is added using a syringe. 0.35 g (0.27 mmol) of **4** are previously dissolved in 20 mL of THF, then added dropwise to the reaction mixture. The crude product is evaporated at the end of 2 hours, then the residue is deposited on a silica column. The product is eluted with dichloromethane and obtained with a yield of 75% (0.30g).

NMR^{1}H 500 MHz (δ ppm, $CDCl_3$, 323K): -2.16 (s, 2H, NH_{pyr}),-0.03 (t, 6H, *J* = 7.0 Hz, $CH_2(CH_3)_i$); 0.57 (d,4H, *Jo* = 13.7 Hz, $(CH_2)_{benz}$), 0.63 (t, 6H, *Jo* = 7.0 Hz, $CH_2(\underline{CH_3})_o$); 1.44 (d, 4H, *Jo* = 13.5 Hz, $(CH_2)_{benz}$); 2.46 (q, 4H, *Jo* = 7.0 Hz, $(CH_2)_iCH_3$); 3.29 (q, 4H, *Jo* = 7.0 Hz, $(CH_2)_oCH_3$); 4.84 (s, 4H, aro_{pick}); 6.61 (d, 4H, *Jo* = 7.6 Hz, aro_{pick}); 6.93 (t, 4H, *Jo* = 7.6 Hz, aro_{pick}); 7.42 (s, 4H, NHCO); 7.51 (td, 4H, *Jo* = 7.6 Hz, *Jm* = 1.2 Hz, aro_{pick}); 7.55 (td, 4H, *Jo* = 7.3 Hz, *Jm* = 1.6 Hz, aro); 7.87 (td, 4H, *Jo* = 7.3 Hz, *Jm* = 1.0 Hz, aro); 7.89 (dd, 4H, *Jo* = 8.4 Hz, aro); 8.69 (s, 4H, β-pyr); 8.70 (dd, 4H, *Jo* = 8.4 Hz, *Jm* = 1.0 Hz, aro); 8.98 (s, 4H, β-pyr).

NMR^{13}C125MHz (δ ppm, $CDCl_3$, 323K): 12.9; 13.7; 40.5; 59.5; 60.3; 60.9; 115.2; 122.8; 123.9; 126.1; 127.2; 128.6; 130.3; 130.6; 132.4; 133.0; 133.4; 134.0; 134.9; 135.9; 139.0; 165.1; 168.9; 169.7.

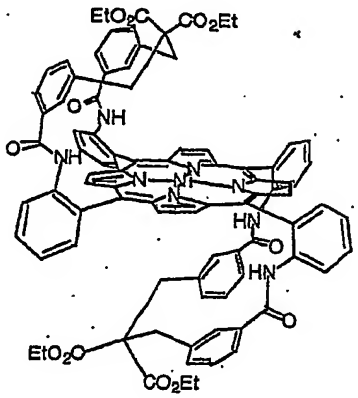
UV-*vis* (CH_2Cl_2, λ/nm ($10^{-3}.\varepsilon$, $M^{-1}.cm^{-1}$)): 422 (433.5); 516 (17.4); 550 (4.8); 590 (5.6); 647 (1.4).

Mass spectrometry (FAB): m/z = 1458.6 $[M]^+$.

Elemental analysis: for $C_{90}H_{74}N_8O_{12}$, calculated (%): C, 74.06; H, 5.11; N, 7.68; found (%): C, 74.25; H, 5.35; N, 7.30.

Infrared: (KBr, νcm^{-1}): 3426 (NH); 1728 (CO); 1686 (CO).

5Ni (radiocrystallographic structure of Figure 3)



$C_{90}H_{72}N_8NiO_{12}$

MW: 1516.27

45 mg of **5** are dissolved in 1.5 mL of pyridine. An excess of nickel acetate is added. The solution is taken to reflux for 1 hour, then the solvents are evaporated off. The residue is dissolved in CH_2Cl_2, filtered and dried again. After chromatography on a silica column (eluent: CH_2Cl_2/MeOH (98/2), the desired product is obtained with a yield of 98%).

NMR ^1H MHz (δ ppm, CDCI3, 323K): 0.16 (t, 6H, *Jo* = 7.1 Hz, $CH_2(CH_3)_i$); 0.70 (t, 6H, *Jo* = 7, Hz, $CH_2(CH_3)_o$); 1.01 (d, 4H, Jo = 13.7 Hz, $(CH_2)_{benz}$); 1.66 (d, 4H, *Jo* = 13.7 Hz, $(CH_2)_{benz}$); 2.81 (q, 4H, *J* = 7.6 Hz, aro_{pick}); 3.41 (q, 4H, *J* = 7.1 Hz, $(\underline{CH_2})oCH_3$); 4.85 (s, 4H, aro_{pick}); 6.67 (d,4H, *J* = 7.6 Hz, aro_{pick}); 6.96 (t, 4H, *J* = 7.6 Hz, aro_{pick}); 7.34 (s, 4H, NHCO); 7.47 (td, 4H, *Jo* = 7.6 Hz, *Jm* = 0.9 Hz, aro_{pick}); 7.59 (td, 4H, *Jo* = 7.7 Hz, *Jm* = 1.4 Hz, aro); 7.77 (dd, 4H, *Jo* = 7.6 Hz, *Jm* = 1.2 Hz, aro); 7.82 (td, 4H, *Jo* = 8.1 Hz, *Jm* = 1.2 Hz, aro); 8.65 (s, 4H, β-pyr); 8.70 (dd, 4H *Jo* = 8.1 Hz, *Jm* = 0.9 Hz, aro); 8.85 (s, 4H, β-pyr).

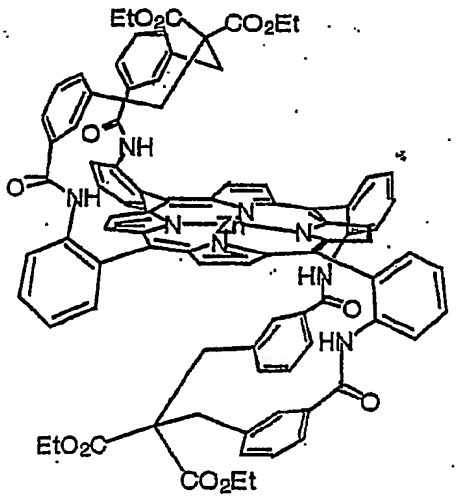
NMR 13C 125 MHz (δ ppm, $CDCI_3$, 323K): 13.1; 13.8; 40.6; 60.6; 61.0; ; 114.5 122.4; 123.8; 126.2; 127.3; 128.7; 130.3; 132.7; 133.0; 133.4; 133.9; 134.1; 136.0; 138.7; 164.7; 170.0.

Mass spectrometry (MALDI/TOF) m/z = 1514.71 $[M]^+$.

Elemental analysis: for $C_{90}H_{72}N_8NiO_{12}\bullet H_2O$, calculated (%): C, 70.45; H, 4.86; N, 7.30; found (%): C, 70.54; H, 5.21; N, 7.06.

Infrared (KBr, νcm^{-1}): 3419 (NH); 1687 (CO).

5Zn



$C_{90}H_{72}N_8O_{12}Zn$

MW: 1522.97

This complex was prepared from **5**, according to the following process. 50 mg of porphyrin base are dissolved in 10 mL of a $CHCl_3$/MeOH mixture (2%). An excess of dihydrated zinc acetate and sodium acetate are added. The solution is taken to reflux for 1 hour, then the solvents are evaporated off. The residue is dissolved in CH_2Cl_2, filtered and dried again. After chromatography on a silica column (eluent: CH_2Cl_2/MeOH (97/3)), a pink-violet product is isolated with a quantitative yield (98%).

NMR ^1H 500 MHz (δ ppm, $CDCl_3$, 323K): -0.40 (d, 4H, *Jo* = 13.0 Hz, $(CH_2)_{benz}$); 0.11 (t, 6H *Jo* = 7.1 Hz; $CH_2(\underline{CH_3})i$); 0.21 (t, 6H, *Jo* = 7.1 Hz, $CH_2(CH_3)_o$); 1.31 (d, 4H, *Jo* = 13.0 Hz, $(CH_2)_{benz}$-); 2.27 (q, 4H, *Jo* = 7.2 Hz, $(\underline{CH_2})_iCH_3$); 2.46 (q, 4H, *Jo* = 7.2 Hz, $(\underline{CH_2})_oCH_3$); 3.82 (s, 4H, aro_{pick}); 6.54 (td, 4H, *Jo* = 7.7 Hz, *Jo* = 1.3 Hz aro_{pick}); 6.94(t, 4H, *Jo* = 7.7 Hz, aro_{pick}); 7.26 (s, 4H, NHCO); 7.55 (td, 4H, *Jo* = 7.6 Hz, *Jm* = 1.2 Hz, aro_{pick}); 7.62 (td, 4H, *Jo* = 8.1 Hz, *Jm* = 1.6 Hz, aro); 7.86 (td, 4H, *Jo* = 8.1 Hz, *Jm* = 1.5 Hz, aro); 7.99 (dd, 4H, *Jo* = 7.5 Hz, *Jm* = 1.2 Hz, aro); 8.69 (dd, 4H, *Jo* = 8.3 Hz, *Jm* = 0.9 Hz, aro); 8.79 (s, 4H, β-pyr); 9.03 (s, 4H, β-pyr).

*NMR ^{13}C 125 MHz (δ ppm, $CDCl_3$, 300K):*13.1; 13.3; 40.5; 60.4; 115.8; 122.4 123.9; 124.7; 127.6; 128.8; 130.1; 132.7; 132.9; 133.0; 133.7; 133.9; 134.5; 139.2; 151.1; 151.9; 164.3; 168.2; 170.1.

Mass spectrometry (MALDI/TOF): m/z = 1522.01 $[M+H]^+$.

Elemental analysis: for $C_{90}H_{72}N_8O_{12}Zn \bullet 2H_2O$, calculated (%): C, 69.34; H, 4.91; N, 7.19; found (%): C,69.09; H, 4.90; N, 7.43.

Infrared (KBr, νcm^{-1}):3420 (NH); 1728 (CO); 1683 (CO)

Preparation of compounds 11, 12 and 13 (see Figure 6)

Experimental conditions:

715 mg (31.1 mmol) of sodium is dissolved in 45 mL of absolute ethanol in a 250-mL flask under argon. After 1 hour, ethyl cyanoacetate (3.32 mL; 31.1 mmol) is added using a syringe. The solution whitens after a few minutes. The mixture is maintained under stirring for 1 hour. 400 mg (0.311 mmol) of **4** are previously dissolved in 70 mL of THF, then added dropwise to the reaction mixture. The crude product is evaporated after 12 hours, then the residue is precipitated from a mixture of dichloromethane and pentane. The precipitate is dissolved in a minimum amount of dichloromethane in order to be deposited on a silica column. A progressive rise to 0.2 % methanol makes it possible to obtain the expected 3 products according to the relative position of the CN and CO_2Et groups. Several chromatography columns are necessary in order to obtain these 3 products of satisfactory purity with the following yields: (8 mg, 2%), (70 mg, 17%) (150 mg, 36%).

The overall yield of the reaction is evaluated at 72 %.

Characterization:

Product obtained at 2%:

NMR ^{1}H (500 MHz, $CDCl_3$, 300 K): δ = 8.96 (s, 4H, β-pyr); 8.75 (d, J = 8.2 Hz, 4H); 8.62 (s, 4H, β-pyr); 7.87 (m, 8H); 7.71 (d, J = 7.9 Hz, 4H); 7.54 (t, J = 7.7Hz, 4H); 7.31 (s, 4H, NH); 7.08 (t, J = 7.7 Hz, 4H); 6.77 (d, J = 7.1 Hz, 4H); 4.42 (s, 4H, $H_{2'}$); 1.90 (q, J = 7.1 Hz, 4H, CH_2CH_3); 1.53 [d, J = 12.9 Hz, 4H, CH_2]; -0.20 [br, 4H, CH_2]; -0.56 (t, J = 7.1 Hz, 6H, CH_2CH_3); -1.96 (s, 2H).

ESI-HRMS: m/z calculated = 1387.48063 $[M+Na]^+$; found 1387.4809.

UV-VIS (CH_2Cl_2, λ nm, 10^{-3} ε, $M^{-1}.cm^{-1}$): 424 (221.0); 518 (14.2); 552 (3.5); 593 (3.8); 651 (0.9).

Product obtained at 17%:

NMR ^{1}H (500 MHz, $CDCl_3$, 300 K): δ = 8.98 (s, 2H, β-pyr); 8.96 (s, 2H, β-pyr); 8.84 (d, J = 8.2 Hz, 2H); 8.70 (d, J = 4.7 Hz, 2H, β-pyr); 8.62 (d, J = 4.7 Hz, 2H, β-pyr); 8.52 (d, J = 8.2 Hz, 2H); 8.34 (d, J = 7.4 Hz, 2H); 7.92 (t, J = 7.9 Hz, 2H); 7.83 (t, J = 7.9 Hz, 2H); 7.75 (d, J = 7.9 Hz, 2H); 7.71 (t, J = 7.9 Hz, 2H); 7.61 (d, J = 7.7

Hz, 2H); 7.57 (s, 2H, NH); 7.54 (d, J = 7.4 Hz, 2H); 7.40 (t, J = 7.4 Hz, 2H); 7.08 (t, J = 7.7 Hz, 2H); 6.94 (t, J = 7.7 Hz, 2H); 6.89 (s, 2H, NH); 6.74 (d, J = 7.7 Hz, 2H); 6.38 (d, J = 7.7 Hz, 2H); 5.18 (s, 2H, $H_{2'}$); 3.58 (s, 2H, $H_{2'}$); 2.97 [q, J = 7.1 Hz, 2H, $(CH_2)_eCH_3$]; 2.10 [q, J = 7.1 Hz, 2H, $(CH_2)_iCH_3$]; 1.77 [d, J = 12.9 Hz, 2H, CH_2]; 1.39 [d, J = 12.9 Hz, 2H, CH_2]; 0.83 [d, J = 12.9 Hz, 2H, CH_2]; 0.11 [t, J = 7.1 Hz, 3H, $CH_2(CH_3)_e$]; -0.56 [t, J = 7.1 Hz, 3H, $CH_2(CH_3)_i$]; -1.91 [d, J = 12.9 Hz, 2H, CH_2]; -2.04 (s, 2H).

ESI-HRMS: m/z calculated = 1387.48063 $[M+Na]^+$; found 1387.4804.

UV-VIS (CH_2Cl_2, λ nm, 10^{-3} ε, $M^{-1}.cm^{-1}$): 424 (308.5); 518 (17.1); 552 (4.0); 592 (4.9); 648 (1.3).

FTIR (KBr, cm^{-1}): 2240 (ν_{CN}).

Product obtained at 36%:

NMR ^{1}H (500 MHz, $CDCl_3$, 300 K): δ = 9.06 (s, 4H, β-pyr); 8.71 (s, 4H, β-pyr); 8.54 (d, J = 8.2 Hz, 4H); 8.10 (d, J = 7.4 Hz, 4H); 7.89 (t, J = 7.9 Hz, 4H); 7.62 (m, 8H); 7.08 (s, 4H, NH); 6.94 (t, J = 7.4 Hz, 4H); 6.40 (d, J = 7.7 Hz, 4H); 3.87 (s, 4H, $H_{2'}$); 2.94 (q, J = 7.1 Hz, 4H, CH_2CH_3); 1.54 [d, J = 12.4 Hz, 4H, CH_2]; 0.10 (t, J = 7.1 Hz, 6H, CH_2CH_3); -1.41 [d, J = 12.4 Hz, 4H, CH_2]; -1.96 (s, 2H).

ESI-HRMS: m/z = calculated 1387.48063 $[M+Na]^+$
found 1387.4784

NMR ^{13}C (125 MHz, $CDCl_3$, 300 K): 165.6; 164.3; 138.7; 135.9; 134.2; 133.7; 132.8; 132.3; 131.4; 130.0; 129.1; 128.6; 128.0; 125.3; 124.2; 123.6; 115.3; 115.1; 61.6; 53.8; 40.2; 12.8.

UV-VIS (CH_2Cl_2, λ nm, 10^{-3} ε, $M^{-1}.cm^{-1}$): 424 (353.2); 518 (18.3); 553 (4.0); 590 (5.3); 647 (1.6).

FTIR (KBr, cm^{-1}): 2240 (ν_{CN}).

Preparation of compound 19 (see Figure 9)

Experimental conditions:

215 mg (9.37 mmol) of sodium are dissolved in 12 mL of absolute ethanol in a 250-mL flask under argon. After stirring for 1 hour and 20 minutes, ethyl cyanoacetate (1.00 mL; 9.37 mmol) is added using a syringe,. The solution whitens after a few minutes. The mixture is maintained under stirring for 1 hour. 120 mg (0.0937 mmol) of **17** (obtained from αβαβ TAPP, according to the protocol used for preparing **4** as described above) are previously dissolved in 30 mL of THF, then added dropwise to the reaction mixture over 30 minutes. The crude product is evaporated after 12 hours and washed with distilled water (3 × 50 mL). The aqueous phase is then precipitated from a mixture of dichloromethane and pentane. The precipitate is filtered and redissolved in a minimum amount of dichloromethane in order to be deposited on a silica column. A progressive rise to 0.2 % methanol makes it possible to obtain product **19** with a yield of 60 % (75 mg).

17: NMR ^{1}H (300 MHz, $CDCl_3$, 323 K): δ = 8.95 (s, 8H, β-pyr); 8.84 (d, *J* = 8.5 Hz, 4H, aro); 8.07 (d, *J* = 8.5 Hz, *J* = 1.2 Hz, 4H, aro); 7.92 (t, *J* = 8.5 Hz, *J* = 1.2 Hz, 4H, aro); 7.59 (t, *J* = 8.5 Hz, 4H, aro); 7.46 (s, 4H, NH); 6.77 (d, *J* = 7.5 Hz, 4H, aro); 6.65 (d, *J* = 7.5 Hz, 4H, aro); 6.57 (t, *J* = 7.5 Hz, 4H, aro); 6.30 (broad s, 4H, aro); 3.35 (s, 8H, CH_2); -2.51 (s, NH, 2H).

19: NMR ^{1}H (300 MHz, $CDCl_3$, 323 K): δ = 9.14 (m, 2H, aro); 9.08 (s, 4H, β-pyr); 8.93 (s, 4H, β-pyr); 8.76 (s, 2H, aro); 8.07 (d, *J* = 7.3 Hz, 2H, aro); 7.93 (m, 8H, aro); 7.79 (m, 6H, aro); 7.60 (t, *J* = 7.4 Hz, 2H, aro); 7.52 (t, *J* = 7.4 Hz, 2H, aro); 7.17 (m, 8H, aro + NH); 4.94 (s, 2H, H); 4.86 (s, 2H, H); 2.20 (m, 4H, (CH_2)); 1.62 (m, 4H, (CH_2)); -0.03 (m, br, 4H, CH_2CH_3); -1.46 (t, *J* = 6.9 Hz, 6H, CH_2CH_3); -2.09 (s, 2H).

Metallation of porphyrin by Bismuth in ethanol

The usefulness of this process resides in the use of absolute ethanol. Moreover, the reaction takes place under air and at ambient temperature.

30 mg of free-base porphyrin (2.8×10^{-5} mol) is dissolved in 5 mL of ethanol. 30 mg of $Bi(NO_3)_3$, $5H_2O$, (6.2×10^{-5} mol) is added. The solution instantaneously becomes coloured deep green. After stirring for 5 minutes, $NH_{3(g)}$ is bubbled through for a few tens of seconds. The solution is evaporated and the mixture chromatographed on a silica column (eluent: 2% MeOH/dichloromethane). It will be noted that the residue is difficult to dissolve in dichloromethane. Once on the column, little free base to be separated is observed. The product is finally precipitated from a dichloromethane – pentane mixture. The yield is quantitative.